REMARKS

Status of the Claims.

Claims 101-106, 108-141, and 173-175 are pending with entry of this amendment. Claims 101, 106, 173, and 174 are amended herein. The amendments to claim 101, 173, and 174 find support at least at page 24, lines 7-23 of Applicant's specification. Support for the amendment of claim 106 is found at least in the specification in Example 11 at page 32, lines 1-12, which demonstrates that cytotoxic activity is greater in the absence of secreted Hsp47. Therefore, these amendments introduce no new matter.

Applicant appreciates the helpful telephonic interview held with the Examiner on June 1, 2007.

Rejections Under 35 U.S.C. § 102.

Lu and Negrin

Claims 101-110, 118-120, 122-128, 131-141, and 173-175 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Lu and Negrin. Office Action, page 2. The rejection is moot as to claim 107, which has been cancelled, and is respectfully traversed with regard to the remaining rejected claims.

The only pending independent claim, claim 101 recites:

> A composition comprising an ex vivo expanded population of cytotoxic lymphocytes having the ability to kill tumor-associated vasculature cells, and a pharmaceutically acceptable carrier, wherein said population is produced by expanding lymphocytes in a closed system with agitation, and said population has a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1.

In explaining the rejection, the Examiner stated: "[A]pplicant has only indicated that the method of producing the product was different and has not specifically indicated that the product produced by this method produced any structural difference." Office Action, page 3. The different method of production to which the Examiner alluded is recited in claim 101 as "expanding

lymphocytes in a closed system with agitation." As the Examiner recognizes, Lu neither teaches nor suggests this element of claim 101. Claim 101 further recites that the product of this method is a "composition comprising an ex vivo expanded population of cytotoxic lymphocytes" that "has a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask." Lu's "cytokine-induced killer (CIK)" cells were grown in standard tissue culture flasks, as was conventional for lymphocyte cultures in 1994. Thus, claim 101 explicitly excludes Lu's CIK cells.

In the interview, the Examiner indicated that Applicant could not rely on a functional property to distinguish the Lu population. Rather, the Examiner believes that the claims must recite a structural distinction over Lu. However, it is well-settled that an invention may be defined by functional properties. *E.I. du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430 (C.A.F.C. 1988), concerned claims to copolymers that were "in part defined by their properties." *Id.* at 1432. Claim 1, for example, recited a copolymer that has, "when in the form of a film, an Elmendorf tear strength in the range of 150 to 400 grams per mil." Phillips, who was seeking to invalidate this claim for lack of novelty had argued, as does the Examiner, that mere property limitations cannot serve to distinguish the claims from the prior-art copolymers. *Id.* at 1435. The Federal Circuit disagreed stating that "[o]n occasion . . . structure alone may be inadequate to define the invention, making it appropriate to define the invention in part by property limitations." *Id.* The court concluded:

> It is clear, therefore, that the district court correctly regarded the claimed interpolymers as compositions that can be permissibly defined in terms of structure and properties. ***Thus, the issue is not . . . whether one can get a patent on discovering a new property of an old composition of matter. The issue is whether the claimed copolymer as defined in part by various property parameters, is new.***

Id. at 1435-36 (emphasis added).

Similarly, in the present application, the issue is whether the claimed population of cells, as defined in part by the property of enhanced anti-tumor cytotoxic activity, is new. Since the enhancement in cytotoxic activity is defined, in claim 101, as significantly greater than the cytotoxic activity "of a population of cells produced by growing the same lymphocytes in a standard flask," the claimed population of cells unquestionably distinguishes standard flask-grown cell populations, such as Lu's.

Furthermore, as one of skill in art readily appreciates, structure dictates function. Therefore, the fact that the claimed cell population has different properties than that of Lu means that the claimed cell population is necessarily structurally different from that of Lu. This structural difference is expressed, in the pending claims, in terms of a functional limitation. The *DuPont* case discussed above endorses the use of functional or property limitations in claims to define the invention. Indeed, in this case, the court indicated that functional/property limitations could be relied upon as the sole distinction between a claimed invention and a prior-art composition.

The Examiner states that "it can be argued that culturing the cell population by agitation, as claimed, only further purified what was already characterized by Lu *et al.*" Office Action, page 3. This statement demonstrates the error in the rationale underlying the novelty rejection. Even if Applicant had done nothing more than "further purify" Lu's cell population, which is not the case, the resulting composition would be different from Lu's composition, in that it would be further purified. A purer composition is different from a less pure composition. If the claims recite a different composition than that described in a cited reference, the claims cannot properly be rejected for lack of novelty under 35 U.S.C. § 102 over that reference. The pending claims unquestionably recite a different composition than Lu's because the claims explicitly exclude Lu's composition.

In suggesting that Applicant has done nothing more than further purify Lu's cell population, the Examiner relies on claim 101's recitation that the claimed "population has a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing ***the same lymphocytes*** in a standard flask" (emphasis added). As one skilled in the art would readily appreciate, the phrase "the same lymphocytes" refers to the starting population of lymphocytes, prior to ex vivo expansion. The Examiner appears to suggest that two cultures starting with the same lymphocytes, but subjected to different culture conditions would not be expected to produce structurally different cell populations. Nothing could be further from the truth. For example, different culture conditions often favor growth of one or more cell types in a heterogeneous population of cells and/or conversely result in reduced growth or loss of other cell types from the population. Indeed, this phenomenon is the basis of the well-known technique of selecting genetically engineered cells that express a selectable marker. The presence or absence of different cell types in two cell populations represents a material, structural difference between those two cell populations. Even if the two cell populations were to contain exactly the same cell types, but in different proportions, the two cell

populations would be different. For example, a cell population containing 50% cell type A, 25% cell type B, and 25% cell type C would be different from a cell population containing 75% cell type A, 15% cell type B, and 10% cell type C. The first population would not anticipate the second and vice versa.

Moreover, culture conditions can affect the make-up of particular cells, as well as the make-up of a cell population. To illustrate this point, Applicant submits an abstract from Carswell, K.S. & Papoutsakis, E.T., *Biotechnicol. Bioeng.* (May 2000) 328-38 ("Exhibit A"). This abstract describes attempts to culture human T cells in stirred bioreactors for cellular immunotherapy applications. Notably, the authors reported that "[e]xposure to agitation and sparging . . . [caused] a significantly increased rate of downregulation of the interleukin-2 receptor (IL-2R). This finding illustrates that differences in the physical conditions of cultures can lead to clear structural differences, in this case, the amount of IL-2R on the cell surface in the presence of IL-2. As one skilled in the art knowns, such a change would also alter the properties of a cell population grown under such conditions. Specifically, greater downregulation of IL-2R would lead to a commensurate reduction in IL-2 responses mediated by that receptor.

In summary, changes in culture conditions can dramatically affect the structure and properties of the resultant cell populations. Claim 101 recites a composition comprising a cell population that differs from Lu's population in terms of (1) culture conditions ("closed system with agitation"), (2) "a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1," and (3) "the ability to kill tumor-associated vasculature cells."

In maintaining the rejection, the Examiner has disregarded the difference in culture conditions on the ground that the Patent Office bears a lesser burden of proof in making out a *prima facie* case of anticipation. Applicant agrees and notes that this rule of practice is set forth in M.P.E. P. § 2113. In the sentence following this rule, the M.P.E.P. explains:

> Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi,* 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Notably, the M.P.E.P requires "evidence establishing an unobvious difference," not evidence establishing an unobvious ***structural*** difference between the claimed product and the prior art product. The Examiner's emphasis on the need for an explicit structural distinction may be based on the examples discussed in the first few paragraphs of M.P.E.P § 2113 which state, for example:

> The structure implied by the process steps should be considered when assessing the patentability of product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made, or where the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product. See, e.g., *In re Garnero*, 412 F.2d 276, 279, 162 USPQ 221, 223 (CCPA 1979) (holding "interbonded by interfusion" to limit structure of the claimed composite and noting that terms such as "welded," "intermixed," "ground in place," "press fitted," and "etched" are capable of construction as structural limitations.)

Applicant respectfully submits that this passages discusses the need for a structural distinction because the difference conferred by the process in the *Garnero* case was, if anything, structural.

However, the second-to-the-last paragraph of this section indicates that applicants can also rebut a *prima facie* case by coming forward with evidence establishing an unobvious ***functional*** difference between the claimed product and the prior-art product. In particular, this paragraph states:

> *Ex parte Gray*, 10 USPQ2d 1922 (Bd. Pat. App. & Inter. 1989) (The prior art disclosed human nerve growth factor (b-NGF) isolated from human placental tissue. The claim was directed to b-NGF produced through genetic engineering techniques. The factor produced seemed to be substantially the same whether isolated from tissue or produced through genetic engineering. While the applicant questioned the purity of the prior art factor, no concrete evidence of an unobvious difference was presented. ***The Board stated that the dispositive issue is whether the claimed factor exhibits any unexpected properties compared with the factor disclosed by the prior art. The Board further stated that the applicant should have made some comparison between the two factors to establish unexpected properties since the materials appeared to be identical or only slightly different.***).

(Emphasis added.) In view of the *Gray* case, the Examiner's insistence on a structural difference between the claim cell population and that disclosed in Lu is contrary to settled law.

Moreover, the evidence that the Board indicated, in *Gray*, as necessary to rebut a *prima facie* case is already of record in the present application. The Board required "a comparison

between the two factors to establish unexpected properties." Applicant's specification contains exactly this evidence. In particular, as shown in Figure 2B, cells grown in a closed system with agitation show significantly higher specific lysis of OCI-Ly8 B-cell lymphoma cells, as measured in a ^{51}Cr-release assay when added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1. The closed system-grown cells had a 35% higher specific lysis of OCI-Ly8 B-cell lymphoma cells than cells grown in standard flasks. This is a material difference in the context of the invention, which was to prepare a population of cells suitable for immunotherapy. More specifically, a significant increase in cytotoxic activity of the cells allows the clinician to reduce the number of cells that needed to be infused to treat a patient's cancer, which reduces the risk of stroke.

This difference in anti-tumor cytotoxic activity could not have been predicted, given that, before the priority date of the present application application, lymphocytes were not standardly grown in closed systems with agitation, and efforts to expand cytotoxic lymphocytes in bioreactors were not generally successful. Exhibit A, which was published between the priority date and filing date of the present application, evidences that, under the disclosed conditions, T cells and T cell lines either grew less well in with agitation and/or in bioreactors, were more fragile, or showed an increased rate of down-regulation of IL-2 receptor. If anything, these results would suggest that the activity of a cytotoxic T cell population grown in a closed system with agitation would be reduced, rather than increased, compared to standard flask-grown cells. Accordingly the requirement that "specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask" recited in claim 101 represents an unexpected, as well as material, difference over the cited art. Thus, Applicant has "come forward with evidence establishing an unobvious difference between the claimed product and the prior art product," as required by M.P.E.P. §2113; and this evidence is precisely the type of comparative evidence that the Board has indicated as sufficient to overcome a *prima facie* case of anticipation in *In re Gray*. Applicant has thus fully rebutted the *prima facie* case based on Lu.

Claim 101 defines a population of cells that is produced by a materially different method and has a materially different anti-tumor activity. For this reason, claim 101 clearly distinguishes the Lu reference.

Claim 101 also distinguishes the Lu reference based on its recitation of "the ability to kill tumor-associated vasculature cells." The ability to kill tumor-associated vasculature cells, while sparing normal vasculature cells, had never previously been described for any population of cells. The Examiner's argument that this property was inherent in Lu's cells cannot properly be

maintained now that claim 1, on its face, defines a population of cells that is materially different from Lu's. According to the M.P.E.P., a "prima facie case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product." M.P.E.P. § 2112.01 (citing *In re Best*, 562 F.2d 1252, 1255 (C.C.P.A. 1977)). Applicant has meet this burden by establishing that the claimed population is different from Lu's with respect to anti-tumor activity. As those of skill readily appreciate, once it is established that Lu's cells represented a different population than the claimed population, there is simply no credible scientific basis for assuming that Lu's cells ***necessarily*** had "the ability to kill tumor-associated vasculature cells," as recited in claim 101. It is well-settled that "[i]nherency . . . may not be established by probabilities or possibilities." *Continental Can Co. USA, Inc.* v. *Monsanto Co.*, 948 F.2d 1265, 1268-69 (Fed. Cir. 1991) (quoting *In re Oelrich*, 666 F.2d 578,581 (C.C.P.A. 1981)). For this additional reason, then, claim 101 is clearly patentable over Lu.

All of the remaining rejected claims depend, directly or indirectly, from claim 101 and are thus distinguished from Lu for at least the reasons discussed above. Accordingly, withdrawal of the § 102 rejection over Lu is respectfully requested.

Alvernas et al.

Claims 101-110, 122-128, 131-141, and 173-175 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Alvernas et al. Office Action, page 4. The rejection is moot as to claim 107, which has been cancelled, and is respectfully traversed with regard to the remaining rejected claims.

Alvernas describes studies performed on "CIK" cells, which, as the abstract indicates had been previously described by the Negrin laboratory at Stanford University. This is the same laboratory that published Lu and Negrin earlier. Alvernas teaches that the disclosed CIK cells were "generated through the sequential stimulation of human mononuclear cells with interferon-γ, the anti-CD3 MAb OKT3 and IL-2" and describes no variation in the procedure for producing CIK cells that is disclosed in the Lu reference. Accordingly, one skilled in the art would conclude that Alvernas' cells were grown in standard tissue culture flasks and had relatively low anti-tumor cytotoxic activity.

Therefore, the distinctions discussed above for the Lu reference also apply to the Alvernas reference. First, claim 101 recites a cell population "produced by expanding lymphocytes in a closed system with agitation," rather than in a standard flask. Second, claim 101 recites that

this cell "population has a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1." Finally, the record manifestly fails to provide any basis for assuming that Lu's cells ***necessarily*** had "the ability to kill tumor-associated vasculature cells." Because Alvernas fails to teach these elements of claim 101, explicitly or inherently, claim 101 clearly distinguishes Alvernas.

The remaining rejected claims are distinguished for Alvernas at least by virtue of their dependence from claim 101. Withdrawal of the § 102 rejection over Alvernas is therefore respectfully requested.

Rejections Under 35 U.S.C. § 112, First Paragraph.

Claims 101-106, 108-141, and 173-175 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Office Action, page 5. The rejection is respectfully traversed.

In support of the rejection, the Examiner states:

> The specification teaches that the cell population of the instant invention has cytotoxic activity against the tumor target OCI-Ly8. The specification does support a cell line that comprises a general cytolytic activity as instantly claimed.

Id. Presumably, the Examiner intended to say that the specification does ***not*** support a cell line that comprises a general cytolytic activity as instantly claimed. Claim 101 has been amended to recite a population that "has a cytotoxic activity characterized in that specific lysis of OCI-Ly8 B-cell lymphoma cells significantly exceeds that of a population of cells produced by growing the same lymphocytes in a standard flask, as measured in a ^{51}Cr-release assay wherein the population is added to said OCI-Ly8 B-cell lymphoma cells at a ratio of 10:1." Withdrawal of the rejection is therefore respectfully requested.

Conclusion.

In view of the foregoing, Applicant believes that all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicant requests a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 267-4160.

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EXHIBIT A

1: Biotechnol Bioeng. 2000 May 5;68(3):328-38.

Culture of human T cells in stirred bioreactors for cellular immunotherapy applications: shear, proliferation, and the IL-2 receptor.

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Ex vivo expansion of T cells is a key step of many cellular immunotherapy protocols, which require large numbers of immune cells to eradicate malignant or virally infected cells. The use of stirred culture systems for T cell expansion offers many potential advantages over the static culture systems commonly used today, including homogeneity of culture conditions, ease of sampling, and implementation of control systems. Primary human T cells as well as the transformed TALL103/2 T cell line were cultured in 100-mL spinner flasks as well as 2-L bioreactors to investigate the effects of shear forces produced by agitation and sparging-based aeration on the expansion of T cells. Primary T cells could be successfully grown at agitation rates of up to 120 rpm in the spinner flasks and to 180 rpm in the bioreactors with no immediate detrimental effects on proliferation. Exposure to agitation and sparging did, however, cause a significantly increased rate of downregulation of the interleukin-2 receptor (IL-2R), resulting in lower overall expansion potential from a single stimulation as compared to static controls, with faster IL-2R downregulation occurring at higher agitation rates. For the primary T cells, no significant effects of agitation were found on expression levels of other key surface receptors (CD3, CD28, or CD62L) examined. No significant effects of agitation were observed on primary T cell metabolism or levels of cellular apoptosis in the cultures. The TALL103/2 T cell line was found to be extremely sensitive to agitation, showing severely reduced growth at speeds above 30 rpm in 100-mL spinner flasks. This unexpected increased fragility in the transformed T cell line as compared to primary T cells points out the importance of carefully selecting a model cell line which will accurately represent the characteristics of the cell system of interest.

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